

REMARKS

The Office Action dated July 28, 2004 has been carefully considered. Claims 1, 10 and 18-21 have been amended. Claims 1, 4, and 7-24 are pending in this application.

35 U.S.C. § 112, ¶2 Rejections

Claims 1, 4, and 7-24 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, it being asserted that the phrase "wherein not more than about 1.5% of said tocopherol is free tocopherol" lacked "literal support" in the specification as filed.¹ The premise of the rejection is that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey that the inventors had possession of the claimed invention at the time the application was filed.

Reconsideration is respectfully requested.

While Applicants contend the phrase in question did not contravene 35 U.S.C. § 112 (or § 132), the issue is rendered moot as the phrase is no longer employed in the claims as currently amended. Instead, claim 1 and the other independent claims recite a surfactant and specify that the surfactant (1) consist essentially of the covalently linked reaction product of tocopherol and a water-soluble polymer and (2) is at least 99% free of unreacted tocopherol.

The specification unequivocably conveys that the inventors had possession at the time the application was filed of compositions in which tocopherol was covalently linked to a water-soluble polymer (*see, e.g.*, page 12 lines 19-28) including, *inter alia*, tocopherol polyethylene glycol 1000 succinate (TPGS). Since such language uniquely defines the subject matter in question, nothing more would be required in order to comply with 35 U.S.C. § 112.

In the present situation, however, the Examiner has taken the position based on Lambert et al., U.S. Patent No. 6,458,373 B1 (citing col. 22, lines 50-60) that commercially available TPGS is not pure and that there is free tocopherol in solutions of tocopherol esters (such as TPGS), albeit less than 1.0% and, generally less than 0.5%.

¹ The rejection concludes with the statement that "This is New Matter rejection," thereby suggesting the rejection is based on 35 U.S.C. §132, last sentence.

(Official Action, p. 4, 3rd ¶). Applicants submit that Lambert cannot be construed as teaching free tocopherol is *invariably* present in tocopherol esters. Hence the use of such an ester does not inherently extend to the use of free tocopherol or indeed to the use of a mixture of the ester and free tocopherol.

To resolve this issue, the language now utilized in claim 1 and the other independent claims simply makes clear that the Applicants' compositions utilize tocopherol covalently linked to a water-soluble polymer, as disclosed. By additionally specifying the purity of this disclosed component (which purity the Examiner asserts is known), Applicants simply exclude from their claims highly impure preparations which, by reason of those impurities, might hypothetically read on potentially unpatentable subject matter.

Therefore Applicants submit that the claims as currently amended are not a different invention from that originally disclosed and request removal of the objection.

35 USC § 102 Rejections

Claims 1, 4, and 7-24 stand rejected under 35 USC §102(e) as being anticipated by U.S. Patent No. 6,458,373 to Lambert et al. ("Lambert"). The Office Action asserts that Lambert teaches each element of the invention as claimed. It is respectfully suggested that Lambert not only fails to disclose at least one element of the claims as currently presented, but in fact teaches away from the current claims.

Claim 1 as currently amended recites "micelles comprising: (i) a podophyllotoxin . . . and (ii) a surfactant consisting essentially of the covalently linked reaction product of tocopherol and a water-soluble polymer and being at least 99% free of unreacted tocopherol. As a result claim 1 excludes a surfactant with more than 1% unreacted tocopherol. In contrast, Lambert teaches compositions that require the addition of unreacted tocopherol (also referred to as α -tocopherol), and in fact, are entirely based on α -tocopherol emulsions.

The teaching of Lambert is most succinctly recited in the abstract:

"An emulsion of α -tocopherol, stabilized by biocompatible surfactants, as a vehicle or carrier for therapeutic drugs, which is substantially ethanol free and which can be administered to animals or humans various routes is disclosed. Also

included in the emulsion is PEGylated vitamin E. PEGylated α -tocopherol includes polyethylene glycol subunits attached by a succinic acid diester at the ring hydroxyl of vitamin E and serves as a primary surfactant, stabilizer and a secondary solvent in emulsions of α -tocopherol."

As indicated, α -tocopherol is a required component to the emulsion of Lambert. PEGylated α -tocopherol (of which TPGS is one) is also contemplated as a component but serves the role of primary surfactant and secondary solvent in emulsions of α -tocopherol. In Lambert, PEGylated α -tocopherol, and surfactants in general, are added to stabilize the α -tocopherol emulsion. No where in this abstract, or in the specification, is a formulation disclosed or suggested that omits α -tocopherol from the formulation. As further illustration of this point, the specification states in the Summary of the Invention:

"In order to meet these needs, the present invention is directed to pharmaceutical compositions including: α -tocopherol, a surfactant or mixtures of surfactants, with and without an aqueous phase, and a therapeutic agent wherein the composition is in the form of an emulsion, micellar solution or a self-emulsifying drug delivery system."

Lambert, Col. 3, lines 46-52. Finally, the formulations disclosed in Lambert each contain α -tocopherol as a separate and distinct ingredient from TPGS.

The specification also contains numerous affirmative statements that support the conclusion that Lambert teaches away from the invention as currently amended. For example, the Lambert specification states: "The α -tocopherol concentration of the emulsions of this invention can be from about 2 to about 10% w/v. The ratio of α -tocopherol to TPGS is optimally from about 1:1 to about 10:1 (w/w). Column 10, lines 1-4. This indicates that Lambert teaches that it is optimal to have as much as ten times as much α -tocopherol than TPGS, but not optimal to have less α -tocopherol than TPGS. Further support for this conclusion is found at column 23, line 65 referring to a "high ratio of TPGS to α -tocopherol" (0.425/0.325) as possibly responsible for Paclitaxel crystallization. As another example, Lambert discusses why TPGS is a desirable additive to an α -tocopherol emulsion, "The utility of TPGS in α -tocopherol emulsions is a synergy of several desirable

characteristics . . ." Column 15, lines 62-63. Again, these are examples that make clear that the teaching of Lambert with respect to TPGS is as an additional ingredient in an α -tocopherol emulsion.

The Office Action relies on column 22, lines 50-60 of Lambert ("Example 26") for teaching a concentration of free α -tocopherol in the solution of less than 1.0%, generally less than 0.5%. The Applicants suggest that Example 26 is not a Paclitaxel formulation, or any formulation, within the context of the disclosure, but rather a stand alone experiment that merely discloses the α -tocopherol concentration in TPGS. As can be seen, the specification does not indicate that any solutions were prepared in this example, nor was any paclitaxel added. Example 26 may be included solely to indicate that TPGS is not a significant source of α -tocopherol, but whatever the reason, Example 26 does not anticipate the invention as currently claimed.

In sum, Lambert teaches a formulation requiring α -tocopherol and the current invention claims a composition that restricts the presence of α -tocopherol by several orders of magnitude compared to Lambert. The Office Action has relied on Example 26 of Lambert as fact that TPGS necessarily includes a certain minimum amount of α -tocopherol. While this interpretation is not accepted by the Applicant, the claims have been amended to be consistent with this interpretation by reciting a surfactant being at least 99% free of unreacted tocopherol. Submitted herein is a third declaration evidencing the surprising nature of the present invention in light of the teachings of Lambert.

For all the foregoing reasons, the Applicants submit that Claims 1, 4, and 7-24 are in condition for allowance. The Examiner is invited to contact the undersigned should he believe that this would expedite prosecution of this application. It is believed that no fee is required. The Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 13-2165.

Respectfully submitted,



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